

VASCEPA® (icosapent ethyl) Fact Sheet and Glossary

What is VASCEPA® (vas-EE-puh) (icosapent ethyl)?

VASCEPA is a single-molecule, FDA-approved medicine in an oral capsule.

The active ingredient in VASCEPA is icosapent ethyl. VASCEPA has a unique¹ chemical structure and clinical effect that has not been shown for any other product. The FDA has designated VASCEPA as a new chemical entity.

VASCEPA is only available by prescription and is unique in its clinical effect and safety profile. It is also distinct in its purity, manufacturing processes, stability, and FDA review and oversight. Manufacturing processes, encapsulation and packaging, qualified to meet or exceed FDA drug standards, are designed to ensure VASCEPA consistency and stability. This is important because, if damaged, the safety and efficacy of the active ingredient can vary and is highly vulnerable to derivatives and oxidation/spoilage. Stringent and complex FDA-regulated manufacturing processes are specially designed to effectively eliminate impurities and isolate the single molecule active ingredient from degradation while ensuring that it is unadulterated.

Referring to VASCEPA as “fish oil” as that term is generally understood, is factually incorrect, misleading and could result in patient confusion, treatment errors and potential patient harm if they believe that dietary fish oil supplements have the same clinical effects and safety profile as VASCEPA. Dietary fish oil supplements, like any of the dietary supplements, are classified as food not as drugs and are not subject to FDA drug standards.

In contrast, dietary fish oil supplements typically contain a very small amount of EPA. Fish oil that claims to contain higher levels of EPA have been synthetically manufactured by varied processes.

Why was VASCEPA developed?

VASCEPA® (icosapent ethyl) is a **new generation medicine** being advanced to address unmet needs in **preventive cardiovascular care** and to address unmet needs in lowering the risk of pancreatitis.

VASCEPA is a proven medication developed and clinically studied over more than a decade at an aggregate cost in excess of \$500 million.

Recent clinical trial results demonstrate that VASCEPA lowers major adverse cardiovascular events (MACE) in at-risk patients studied in that trial, positioning VASCEPA to become a new treatment option to reduce cardiovascular risk. Amarin intends to seek expanded labeling for VASCEPA based on this data. The FDA has not reviewed and opined on a new drug application relating to this cardiovascular risk data.

The medicine is approved today along with diet and exercise for the treatment of very high triglyceride levels in adults, a medical condition which can lead to pancreatitis.

¹ Brinton and Mason Lipids in Health and Disease (2017) 16:23
<https://lipidworld.biomedcentral.com/articles/10.1186/s12944-017-0415-8>

Glossary

atherosclerosis: Cholesterol-lipid-calcium deposits in the walls of arteries that can restrict blood flow. Atherosclerosis is a progressive disease. If left untreated, lesions may thicken and form fibrous plaques, nearly completely blocking blood flow and causing ischemia. If a plaque ruptures, the affected blood vessel may close, and organs or tissues may infarct.

blood lipids (or blood fats): Blood lipids are mainly fatty acids and cholesterol. The presence of elevated or abnormal levels of lipids in the blood is a major risk factor for cardiovascular disease.

cardiovascular disease (CVD): Cardiovascular disease generally refers to conditions that involve narrowed or blocked blood vessels that can lead to a heart attack, chest pain (angina) or stroke. Cardiovascular disease is the #1 killer in the United States (one death every 38 seconds).

cardiovascular outcome trial (CVOT): Clinical trials that assess the effects of a new medication on cardiovascular events such as heart attack and stroke. Typically, these are large-scale and long-term trials that are randomized, double-blinded, and placebo-controlled.

cardiovascular risk factors: Conditions or habits that are associated with a greater likelihood of developing a cardiovascular disease. Risk factors for cardiovascular disease include high blood pressure, high LDL (“bad”) cholesterol, high triglycerides (TG), low HDL (“good”) cholesterol, diabetes and prediabetes, smoking, being overweight or obese, physical inactivity, family history of early heart disease, history of preeclampsia during pregnancy, unhealthy diet, being 55 years of age or older.

composite major adverse cardiovascular events (MACE): A cardiac emergency. In recent cardiovascular outcomes trials, the major adverse cardiovascular events included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina.

coronary revascularization: In medical and surgical therapy, revascularization is the restoration of perfusion to the heart. Coronary stents, vascular bypass and angioplasty are examples of coronary revascularization.

DHA: Docosahexaenoic acid (DHA) is a single-molecule, polyunsaturated omega-3 fatty acid. DHA’s molecular structure is a carboxylic acid (*-oic acid*) with a 22-carbon chain (*docosa-* derives from Ancient Greek for 22) and six (*hexa-*) *cis* double bonds (*-en-*); with the first double bond located at the third carbon from the omega end. The structure and function of DHA is unique. In patients with high triglyceride levels, DHA has been associated with increasing LDL (“bad”) cholesterol.

diabetes: Diabetes is a disease in which the body’s ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine.

dietary supplements: Dietary supplements are products classified as food used for nutritional purposes but not intended to treat any medical condition. Dietary supplements do not require advanced FDA approval of efficacy, safety, labeling, manufacturing or marketing claims.

EPA: Eicosapentanoic acid, a single-molecule, polyunsaturated omega-3 fatty acid. The EPA molecule is shorter than DHA. EPA’s molecular structure is a carboxylic acid with a 20-carbon chain (*eicosa-* derives from Ancient Greek for 20) and five (*penta-*) *cis* double bonds; the first double bond is located at the third carbon from the omega end. The structure and function of EPA is unique.

fish oil; A dietary supplement containing dozens of varied ingredients. Like other dietary supplements, fish oil is classified as a food and not intended to treat any medical condition. Typical fish oil consists of approximately 18% EPA, 12% DHA and multiple other ingredients, often including saturated fats. Fish oil dietary supplements have not been shown in clinical study to lower cardiovascular risk and for safety reasons are not intended to use at daily dose levels above 3 grams per day. Dietary supplements which contain DHA may increase LDL (“bad”) cholesterol levels in patients.

HDL cholesterol: High-density lipoprotein, commonly referred to as “good cholesterol.” HDL-C is composed of a high proportion of protein with little triglyceride and cholesterol and that is correlated with reduced risk of atherosclerosis.

LDL cholesterol: Low-density lipoprotein cholesterol are commonly referred to as 'bad' cholesterol. Elevated LDL-C levels are associated with an increased risk of heart disease. Lipoproteins, which are combinations of fats (lipids) and proteins, are the form in which lipids are transported in the blood.

myocardial infarction: Myocardial infarction is another term for heart attack.

over-the-counter-drugs (OTC): Previous prescription drugs which the FDA deems after years of use to be safe for use without prescription and without medical supervision. While OTC is a term used by some people to refer to dietary supplements because they often are presented near each other in retail stores, OTC drugs and dietary supplements are very different. Dietary supplements are not and were never classified as drugs or reviewed for safety or efficacy like drugs or reviewed for manufacturing quality and consistency like drugs. There are no OTC versions of omega-3 products (i.e. fish oil is not an OTC product per regulatory guidelines, fish oil is classified as food and regulated as food not as a drug)

prescription drug or prescription medicine: Therapy approved by regulatory authorities (FDA in the U.S.) for treating medical conditions.

primary prevention (1^o): Preventing illness in an unaffected patient or healthy population. Primary prevention of cardiovascular disease aims to reduce the risk of heart attack, stroke, and other cardiovascular events in those who have not yet experienced a clinical manifestation of the disease.

P-value: The probability of a finding occurring by random chance rather than as a result of the treatment being tested. The P value can be thought of as a means of determining whether an observed effect is real or a chance occurrence. A P value of 0.05 is a commonly used cutoff for statistical significance. In a clinical trial, a P value of < 0.05 often confirms a statistically significant difference in the treatment groups.

REDUCE-IT: REDUCE-IT is a landmark global outcomes study that investigated the cardioprotective effects of 4 grams daily VASCEPA. The study commenced in late 2011 with topline results announced September 24, 2018. In REDUCE-IT, VASCEPA was studied as an add-on to statin therapy to reduce the risk of cardiovascular (CV) events in patients with bad (LDL) cholesterol between 41-100 mg/dL (median baseline LDL-C 75 mg/dL) who have other CV risk factors, including elevated triglyceride levels between 150-499 mg/dL (median baseline TG 216 mg/dL) and diabetes or previous cardiovascular (CV) events. The REDUCE-IT trial was an event-driven CV outcomes study. It was not designed to validate the effect of lowering triglyceride (a type of fat in the blood) levels or any other lipid biomarker on a stand-alone basis.

relative risk reduction (RRR): The amount of risk reduction relative to the baseline risk.

residual cardiovascular risk: Remaining risk of experiencing a cardiovascular event after a treatment has effectively reduced a risk factor. For example, significant residual risk of cardiovascular event remains after successfully lowering low density lipoprotein cholesterol levels through use of statin therapies.

secondary prevention (2^o): Limiting the risk of recurrence or disease progression in patients who are already afflicted by the illness. Secondary prevention in patients with established cardiovascular disease aims to lower the risk of future cardiovascular events.

statins: Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications. Statins have been found to reduce cardiovascular disease and mortality in those who are at high risk of cardiovascular disease. Statins lower LDL-cholesterol levels and have other pleiotropic effects.

stroke: The sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain. Sudden loss of speech, weakness, or paralysis of one side of the body can be symptoms.

triglycerides: Triglycerides are the main constituents of natural fats and oils, and high concentrations in the blood indicate an elevated risk of cardiovascular disease.

unstable angina: Unstable angina is a condition in which your heart doesn't get enough blood flow and oxygen. It may lead to a heart attack. Angina is a type of chest discomfort caused by poor blood flow through the blood vessels (coronary vessels) of the heart muscle (myocardium).